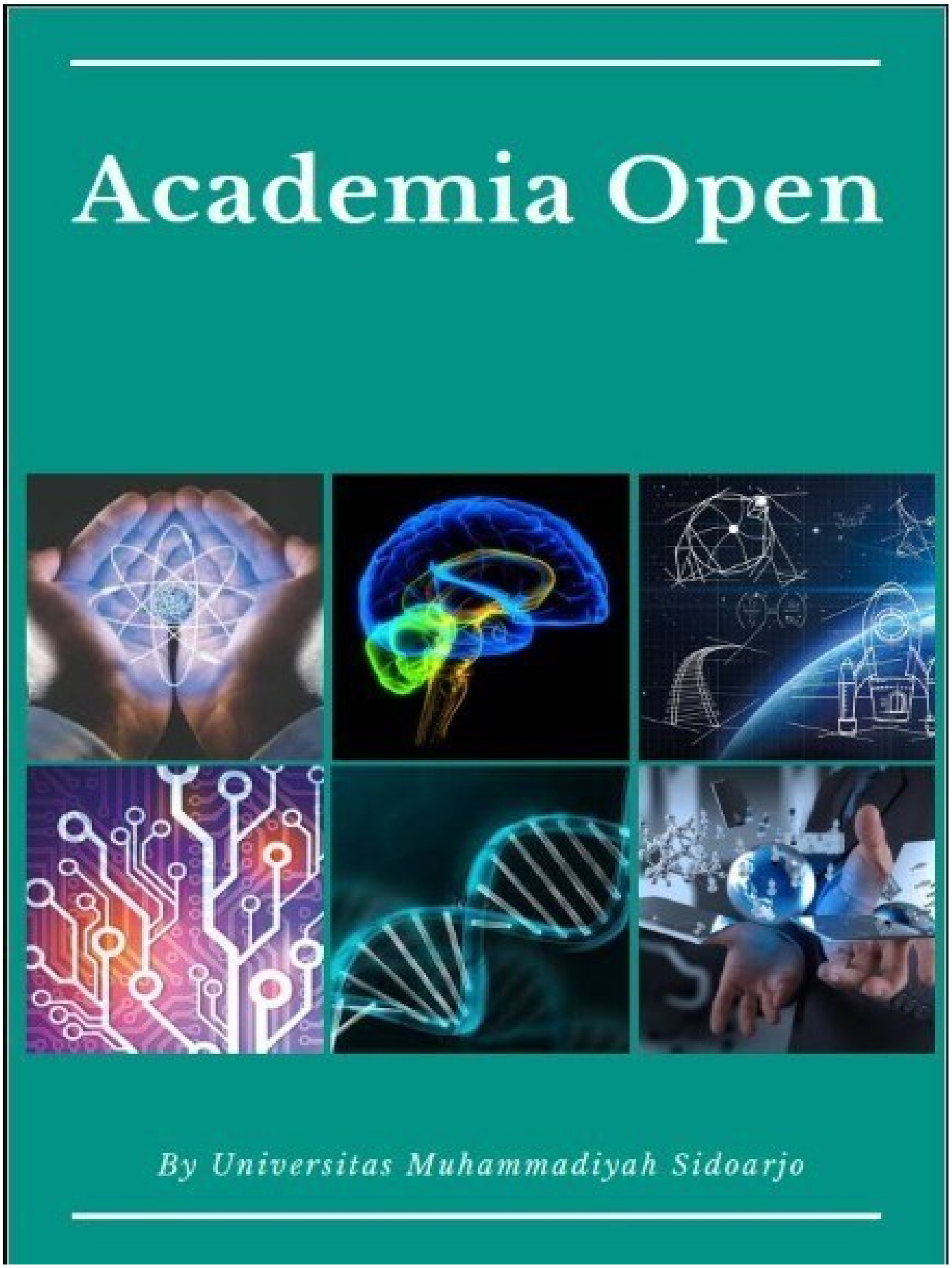
Academia Open

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501



ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

Table Of Contents

Academia Open

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

Originality Statement

The author[s] declare that this article is their own work and to the best of their knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the published of any other published materials, except where due acknowledgement is made in the article. Any contribution made to the research by others, with whom author[s] have work, is explicitly acknowledged in the article.

Conflict of Interest Statement

The author[s] declare that this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright Statement

Academia Open

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

EDITORIAL TEAM

Academia Open

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

Article information

Check this article update (crossmark)

Check this article impact (*)

Save this article to Mendeley

(*) Time for indexing process is various, depends on indexing database platform

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

Can Liquid Biopsy Replace Tissue Biopsy? A Systematic Review and Meta-Analysis of Diagnostic Accuracy in Non-Small Cell Lung Cancer (NSCLC)

Arlinda Silva Prameswari, arlindasilvaprameswari@umsida.ac.id (*)

Departement of Anatomy, Faculty of Medicine, Universitas Muhammadiyah Sidoarjo, Indonesia
Department of Emergency Medicine, Pusura Candi Hospital, Sidoarjo, Indonesia

Fadhilah Arsyil, fadhilaharsyil@umsida.ac.id

Departement of Biochemistry, Faculty of Medicine, Universitas Muhammadiyah Sidoarjo, Indonesia
Department of Emergency Medicine, Pusura Candi Hospital, Sidoarjo, Indonesia

Dwiraras Radityawan, dwirarasradityawan@gmail.com

Department of Pulmonology and Respiratory, Pusura Candi Hospital, Sidoarjo, Indonesia

Erlina Krisdianita Novitasari, erlinakrisdianitanovitasari@umsida.ac.id

Departement of Anatomy, Faculty of Medicine, Universitas Muhammadiyah Sidoarjo, Indonesia
Faculty of Nursing and Health Science, Universitas Muhammadiyah Banjarmasin, Indonesia

(*) Corresponding author

Abstract

General Background: Lung cancer remains a leading cause of malignancy related mortality worldwide, with non-small cell lung cancer as the predominant type. **Specific Background:** Tissue biopsy remains the diagnostic gold standard for NSCLC, yet its invasive procedure, limited sample availability, and reduced capacity to represent tumor heterogeneity restrict clinical utility. **Knowledge Gap:** Although liquid biopsy offers a minimally invasive molecular diagnostic alternative, its diagnostic performance compared with tissue biopsy remains debated. **Aims:** This systematic review and meta-analysis aimed to evaluate the diagnostic accuracy of liquid biopsy versus tissue biopsy in adult patients with NSCLC. **Results:** Following PRISMA guidelines, articles from PubMed, Scopus, ScienceDirect, and Cochrane Library published from 2016 to 2026 were reviewed, with study quality assessed using QUADAS-2 and analysis performed using RevMan 5.4. Fourteen studies involving 3,180 NSCLC subjects were included. Liquid biopsy showed sensitivity ranging from 70.0% to 91.5% with substantial heterogeneity, while specificity remained high from 93.5% to 100% with low heterogeneity. SROC analysis demonstrated excellent diagnostic performance with AUC above 0.90, and no significant publication bias was observed. **Novelty:** This review directly evaluates whether liquid biopsy can serve as an alternative diagnostic approach to tissue biopsy in NSCLC. **Implications:** Liquid biopsy may support, but not replace, tissue biopsy due to variable sensitivity across clinical settings and disease stages.

Highlights:

- Fourteen studies involved 3,180 subjects.
- Specificity remained consistently high across included evidence.
- Variable sensitivity limits standalone clinical use.

Keywords: Liquid Biopsy, Non-Small Cell Lung Cancer, Tissue Biopsy

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

Published Date: 2026-07-14

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

Introduction

Lung cancer dominates cancer mortality globally, with the non-small cell type of lung cancer (NSCLC) accounting for about 85% of total cases.[1] Despite significant advances in drug development in recent years, the prognosis of NSCLC patients remains low with an estimated five-year survival rate of only 28%. Almost half of all patients are detected at an advanced stage, a condition that drastically reduces the effectiveness of curative therapy.[2],[3]

The emergence of various new molecular therapeutic modalities reinforces the urgency of the detection of actionable genetic alterations, in particular EGFR (Epidermal Growth Factor Receptor) mutations in the treatment of NSCLC. Although tissue biopsy is the gold standard, it has several limitation including invasive procedures, limited sample availability, and limited ability to capture tumor heterogeneity.[4] Therefore, many newly diagnosed patients have insufficient tissue specimens for comprehensive molecular analysis.[5]

Liquid biopsy becomes a minimally invasive molecular diagnostic method for NSCLC through analysis of circulating tumor DNA (ctDNA).[6],[7] Innovations in next-generation sequencing and polymerase chain reaction techniques have been shown to increase the ability to detect cancer-related mutations while simultaneously monitoring treatment efficacy.[8] However, the degree of diagnostic precision of liquid biopsy is variable and depends on variables such as specimen type, disease severity, tumor burden, and applied molecular detection technology.[6] Plasma-based ctDNA remains the most popular specimen due to its practical usefulness in diagnosis, however other specimens such as pleural fluid or bronchoalveolar rinse fluid may provide higher effectiveness under special conditions.[4], [7],[10]

Despite the growing evidence supporting the implementation of liquid biopsy for the diagnosis of NSCLC, the debate over its clinical use is still ongoing. This causes tissue biopsy to remain the gold standard for the diagnosis of NSCLC in accordance with the recommendations of applicable international guidelines. A number of systematic reviews have discussed the usefulness of liquid biopsy in NSCLC, but few have evaluated the potential of liquid biopsy as a substitute for tissue biopsy for the diagnosis. In addition, recent developments in ctDNA detection and the emergence of new studies can have a significant impact on the results of diagnostic performance analysis. Therefore, conducting a systematic review and a new meta-analysis of this topic has become an urgent need.

Method

A. Data and methods

We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria in the implementation of this systematic review and meta-analysis.[11] We also pre-registered the study on the PROSPERO platform with the identity number CRD1364024 to strengthen transparency and minimize the risks of bias.[12]

B. Literature retrieval and screening

We conducted a thorough literature search process through PubMed, Scopus, ScienceDirect, and Cochrane Library databases. We applied MeSH terms as well as specific keywords using the following set of search strings: ("Lung Neoplasms "or" Non-Small-Cell Lung Carcinoma") AND ("Liquid Biopsy "or" Circulating Tumor DNA "or" Cell-Free DNA "or" ctDNA") and ("Biopsy "or" Tissue Biopsy") and ("Sensitivity and Specificity "or" Diagnostic Accuracy "or" Diagnostic Performance"). The use of the Boolean operator (AND/OR) serves to link each term in the search. We only include primary research articles published in the period of 2016 to 2026.

Systematic literature review was done using articles meeting the eligibility criteria, which were then separately appraised based on the content of the whole article. Those studies having irrelevant titles and abstracts were excluded during the screening phase. In case of any duplicates found in multiple databases, these articles were excluded during cross-referencing, keeping only one article for analysis. Full-text articles were analyzed to get valuable information. If there were any disagreements between the two reviewers during the inclusion/exclusion process, the decision was taken by the third reviewer.

C. Inclusion and Exclusion Criteria

We included studies that met the following criteria: (i) the manuscript was an original research Article; (ii) the authors composed the work in English; (iii) the research involved patients with non-small cell lung cancer (NSCLC); (iv) the methodology tested for liquid biopsy instruments, such as circulating tumor DNA (ctDNA) or cell-free DNA (cfDNA); (v) the authors used tissue biopsy as a reference standard; and (vi) the report included at least one diagnostic parameter, such as sensitivity, specificity, accuracy of diagnosis, concordance level, or clinical outcome.

We excluded a study if: (i) the author does not clearly set out the main results or provides minimal data; (ii) the manuscript presents data that is impossible to extract or calculate, for example, illustrations without sufficient statistical detail; (iii) the study contains a potential conflict of interest; (iv) the manuscript is not an original work or has not received official publication; (v) the author does not report diagnostic data; or (vi) the article is available only in the form of an abstract or summary table of contents.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

D. Outcomes and Study Quality

The QUADAS-2 instrument assesses the risk of bias through four main dimensions: patient selection, index tests, reference standards, and flow and timing.[13] Researchers assigned low, unclear, or high-risk categories to each of the criteria in the four areas. This evaluation process also considers aspects of the application carefully. We selected studies with a low or unclear risk of bias based on the results of sensitivity analysis or subgroup analysis.

E. Statistical analysis

Review Manager (RevMan) software version 5.4 processed all statistical data in this study. The I^2 statistical value measures the degree of heterogeneity in the range from 0% to 100%. Heterogeneity classification includes low (< 25%), moderate (25% -50%), and high (> 50%) categories. An I2 score above 50% indicates heterogeneity in the data. Researchers used a random effects model to handle studies with high heterogeneity. The effects model remains the preferred choice if heterogeneity is minimal. Meta-analysis of sensitivity and specificity values aimed at measuring diagnostic accuracy. The SROC curve and AUC used to determine the diagnostic performance.[14]

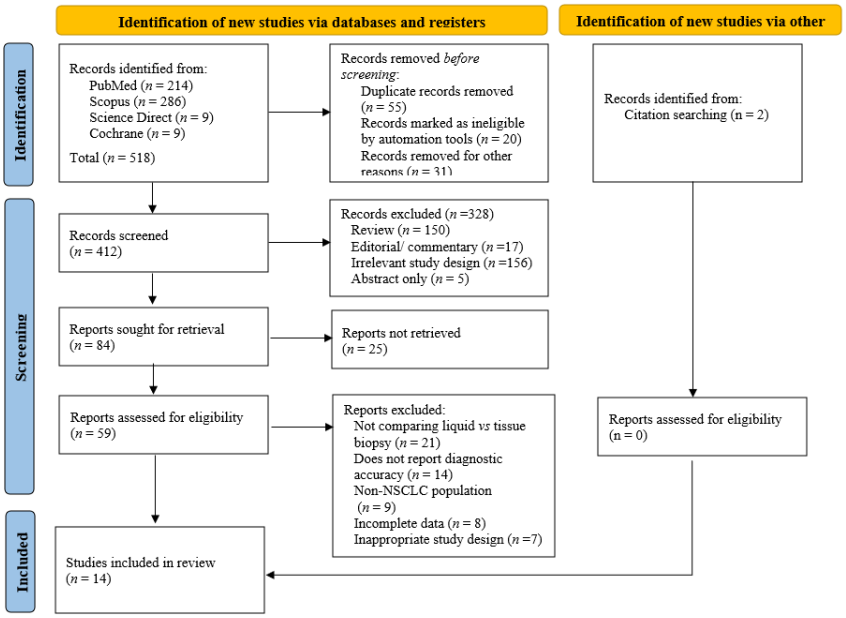


Figure 1. PRISMA flow chart of the record screening process for articles

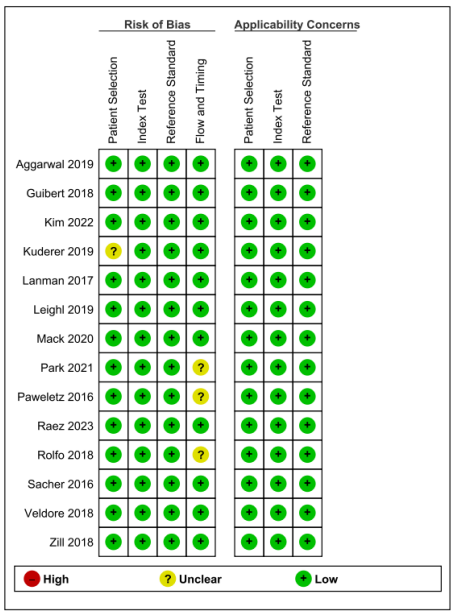


Figure 2. Tabular presentation of the QUADAS-2 assessments in each study

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

Result and Discussion

A. Result

1. Baseline characteristic

In total, 518 records were identified initially, 214 from PubMed, 286 from Scopus, 9 from ScienceDirect, and 9 from the Cochrane Library. The number of articles that underwent further screening was 412 after eliminating duplicates and assessing their titles/abstracts, out of which 328 were excluded because of their review type (n=150), commentaries/editorial (n=17), inappropriate research design (n=156), and were available only as abstracts (n=5). Two more articles identified via the search of citations were also excluded on account of not meeting inclusion criteria. Fourteen articles finally remained for inclusion (Figure 1).

This analysis involved as many as 3180 subjects with NSCLC as a whole. Table 1 below summarizes the detailed information of all selected articles. The evidence assessment categorized all studies into Level II–III cohort studies with recommendation B degrees.[15] Furthermore, QUADAS-2 assessment demonstrated a low risk of bias across all included studies (Table 2).

Table 1. Characteristics and quality articles of included studies

Study	Year	Design	Country	Sample Size	Mean Age (years)	Population	Index Test	Gold Standard	Target Mutation	Clinical Outcome
Aggarwal et al.[16]	2019	Cohort	USA	282	64 ± 10	Advanced NSCLC	ctDNA (NGS)	Tissue biopsy	EGFR, ALK	Treatment selection
Guibert et al.[6]	2018	Cohort	France	89	64 ±9	NSCLC	ctDNA	Tissue biopsy	EGFR T790M	Resistance mutation
Kim et al.[17]	2022	Cohort	Korea	200	62 ±9	NSCLC	Plasma NGS	Tissue biopsy	EGFR	Target therapy
Kuderer et al.[18]	2019	Cohort	USA	177	64 ±11	Advanced NSCLC	ctDNA	Tissue biopsy	Multiple	Real-world outcome
Lanman et al.[19]	2017	Cohort	USA	282	62 ±10	Advanced NSCLC	ctDNA NGS	Tissue biopsy	Multiple genes	Precision oncology
Leighl et al.[20]	2019	Cohort	Canada	300	65 ± 9	Advanced NSCLC	Plasma NGS	Tissue biopsy	EGFR, KRAS	Therapy guidance
Mack et al.[21]	2020	Cohort	USA	323	63 ±10	NSCLC	Liquid biopsy	Tissue biopsy	EGFR, ALK	Therapy response
Park et al.[22]	2021	Cohort	Korea	421	65 ±9	Advanced NSCLC	ctDNA NGS	Tissue biopsy	Multi-gene	Clinical utility
Paweletz et al.[23]	2016	Cohort	USA	102	61 ±10	NSCLC	cfDNA	Tissue biopsy	EGFR	Mutation detection
Raez et al.[24]	2023	Cohort	USA	170	66 ±8	Advanced NSCLC	ctDNA	Tissue biopsy	EGFR	Survival prediction
Rolfo et al.[7]	2018	Cohort	Italy	200	63 ±11	NSCLC	cfDNA	Tissue biopsy	EGFR	Mutation detection
Sacher et al.[25]	2016	Cohort	USA	180	64 ±9	NSCLC	Plasma genotyping	Tissue biopsy	EGFR	Treatment eligibility
Veldore et al.[26]	2018	Cohort	India	163	62 ±11	NSCLC	cfDNA	Tissue biopsy	EGFR	Clinical feasibility
Zill et al.[27]	2018	Cohort	USA	300	65 ±10	Advanced NSCLC	ctDNA NGS	Tissue biopsy	Multi-gene	Comprehensive profiling

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

2. Heterogeneity Analysis

The sensitivity results had considerable heterogeneity (I^2 = 68.4%, p < 0.001), which means that there was some variability among studies. This mean that the ability to detect mutations using liquid biopsy changes from one study to another based on study-specific features, such as research design, patient inclusion criteria, or the stage of cancer involved. On the other hand, specificity had very low heterogeneity (I^2 = 18.7%, p = 0.25) indicating stable performance in correctly identifying mutation-negative patients.

3. Sensitivity and Specificity Analyses

The results of the forest plot analysis revealed that there was variability in sensitivity among the studied articles, which were in the range of 70.0% (95% CI, 60.2%–78.3%) and 91.5% (95% CI, 83.4%–95.9%). The majority of the studied sensitivity was found in the range of 72% to 85%. There was moderate overlap in confidence intervals (Figure 3). These results imply that the ability of liquid biopsy to diagnose target mutations among patients depends on various factors, such as the progression stage of the illness, the amount of tumor mass, and the procedure of identification. In general, it should be concluded that liquid biopsy provides appropriate sensitivity.

On the other hand, specificity was found to be high in all the studies analyzed, with values of between 93.5% (95% CI, 83.5%–96.8%) and 100% (95% CI, 95.5%–100%) (Figure 3). Most of the studies had narrow confidence intervals with high overlap, which implies low variability in the specificity results obtained. The consistent nature of specificity results shows that liquid biopsy has a great capability of identifying those patients that do not have target mutations.

Conclusively, it can be seen that the overall sensitivity of liquid biopsy was moderate to high with wide variability, while specificity showed high results with narrow confidence intervals.

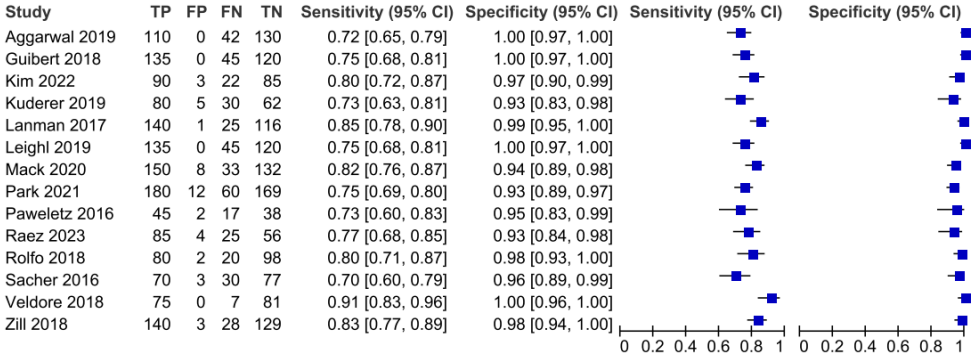


Figure 3. Forest plot of summary sensitivity and specificity of liquid biopsy *Vs* tissue biopsy

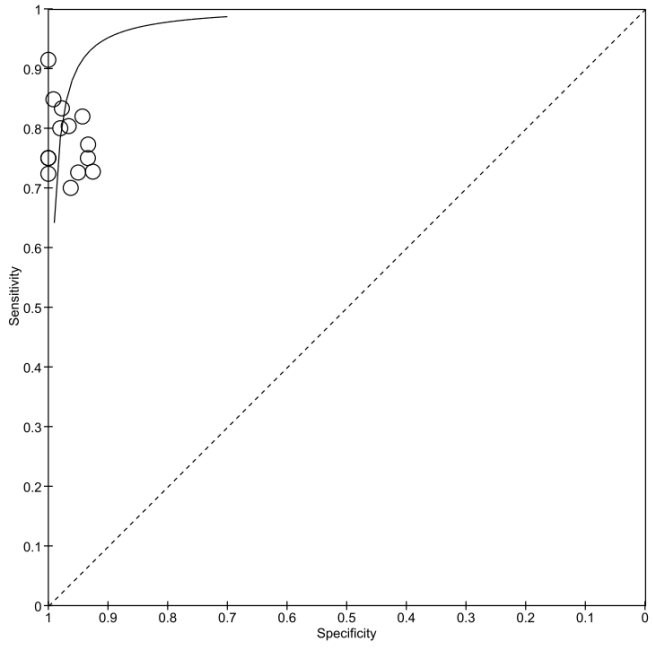


Figure 4. Summary receiver operating curve (SROC) plot

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

As observed in Figure 4, the SROC curve shows that liquid biopsy presents high diagnostic accuracy due to the clustering of the studies near the top left of the plot. This is based on the estimated value of the AUC. However, the heterogeneity observed in the studies, especially for sensitivity, remains a concern.

4. Risk of Bias and Quality Assessment

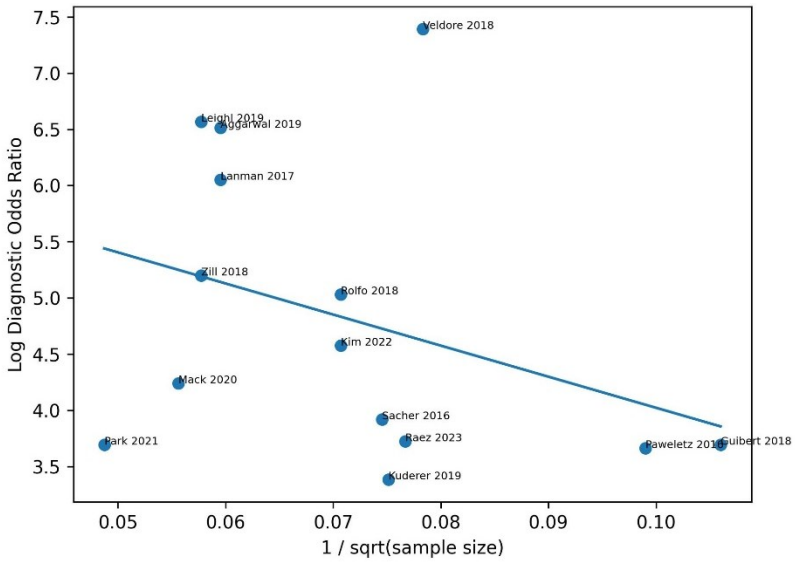


Figure 5. Deeks funnel plot

To check for publication bias within the selected articles, the Deeks funnel plot method was employed. The plot indicated a fairly symmetric distribution with no presence of publication bias. In addition, the Deeks' test of asymmetry did not provide any evidence for publication bias (P>0.05) (Figure 5).

The results suggest that there is a reduced risk of small-study effects and publication bias. This makes the study more reliable and credible. The lack of publication bias further increases the validity of the results, thereby making liquid biopsy applicable for clinical practice.

B. Discussion

This meta-analysis and systematic review update evaluates the diagnostic precision between liquid biopsy and tissue biopsy in adult patients with NSCLC. A total of 14 studies covering 3,180 subjects from six countries were included in the review. The results of the combined data indicate the sensitivity of liquid biopsy ranged from 70.0% (95% CI, 60.2% - 78.3%) to 91.5% (95% CI, 83.4% – 95.9%). Meanwhile, the specificity value was in the range of 93.5% (95% CI, 83.5% - 96.8%) to 100% (95% CI, 95.5% - 100%) for NSCLC identification. The SROC analysis also showed a very high diagnostic accuracy of liquid biopsy. The value of the area under the curve confirms the almost perfect accuracy of detecting such diseases. This Data is consistent with the report of Fernandes et al.[28] on the effectiveness of liquid biopsy in recognizing EGFR mutations in lung cancer. The study reported a combined sensitivity of 68% with a specificity reaching 98%.

The results of the analysis proved that the liquid biopsy was able to efficiently diagnose the majority of mutation cases. However, medical personnel still need to be aware of the potential of false negative results. This false negative condition is common when a liquid biopsy does not show mutations when the tissue sample gives a positive result.[31] Various factors trigger this condition, one of which is the low concentration of ctDNA in the circulating blood. This condition often appears in the early phase of cancer or in tumors that release low concentration of DNA.[33] These findings are consistent with previous studies by Franzi, et al.[29], Mlika, et al.[30], and Wang, et al.[31], All three studies confirmed that tumor burden and circulating ctDNA levels largely determine diagnostic performance. Elevated levels of ctDNA in advanced NSCLC reinforce the basis for the use of liquid biopsy for patients of that stage. Mutation detection will be more optimal in such clinical conditions. In addition, a liquid biopsy becomes a crucial diagnostic alternative if tissue samples are difficult to obtain. This applies to inaccessible tumor sites or invasive procedures that pose a high risk to the patient. This method is also useful when the amount of tissue is insufficient for molecular tests. Liquid biopsy accelerates the detection of mutations before starting therapy and facilitates monitoring of treatment response, drug resistance, and disease progression.[32],[34] Overall, the combination of high specificity and medium sensitivity support the use of liquid biopsy as a functional screening instrument for people with NSCLC.

The term liquid biopsy refers to the examination of biomarkers in circulating blood or other body fluids. The fluid includes pleural fluid, sputum, to the condensate of exhaled breath (EBC). The goal is to identify molecular changes

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

that spur the development of cancer. In the case of lung cancer, this method detects the presence of pathological biomarkers through blood sampling. This process relies on ctDNA as well as CTCs from tumor cells that enter the blood vessels. The use of liquid biopsy is already widespread to recognize genetic variations and determine targeted therapeutic strategies for lung cancer patients.[34]

The process of apoptosis or necrosis releases DNA fragments into the bloodstream. Circulating tumor DNA (ctDNA) arises not only from healthy tissues, but also from malignant cells. We can define ctDNA as a specific element of cell-free DNA (cfDNA). The main source of this type of DNA is the active release as well as the death of tumor cells. Patients with malignant diseases often show elevated levels of ctDNA, although the amount fluctuates depending on the stage and type of cancer. Experts generally use PCR and NGS methods to detect the presence of ctDNA.[21], [35] Several factors affect the diagnostic sensitivity of this method. Such factors include the amount of DNA of tumor origin in the sample, the characteristics of genetic mutations, as well as the analytical capabilities of the detection method.[35] This technical limitation runs the risk of triggering false negative results if ctDNA concentrations are too minimal. Therefore, clinical practitioners should not rely on liquid biopsy as the only single diagnostic tool.

There are several significant methodological advantages regarding this meta-analysis. First, we conducted a systematic and thorough literature search. The process follows a strict registered protocol with clear inclusion and exclusion criteria. Second, the QUADAS-2 instrument is used to mitigate the risk of bias in the selection of all analysis studies. Finally, all selected studies used tissue biopsy as the gold standard in the diagnosis of lung cancer.

There are some limitations to this analysis that require special attention. First, all reference studies came from outside Indonesia. Differences in the prevalence of genetic mutations between populations may affect the relevance of the results if applied to patients in Indonesia. Secondly, the study did not stratify by stage of the disease. ctDNA levels are highly dependent on the phase of tumor development. This causes that the combined sensitivity and specificity values may differ between the early and late stages. These conditions have the potential to limit the generalization of results globally. In addition, this can complicate the clinical implementation of liquid biopsy, in particular when comparing its effectiveness at different stages of NSCLC disease.

The diagnostic precision of liquid biopsy is quite accurate; however, the liquid biopsy test might complement rather than replace tissue biopsy in NSCLC diagnosis, considering its varying sensitivity rate. In future studies, we should consider a more heterogeneous sample that includes the Indonesian population, which would help to assess the effect of genetic and clinical diversity on the diagnostic ability of liquid biopsy in NSCLC patients. Moreover, it is crucial to conduct research on a stage-by-stage basis to achieve a precise evaluation of the sensitivity and specificity of the technique used. It is necessary to standardize diagnostic approaches, including ctDNA testing techniques, such as PCR and NGS. Additionally, it is advisable to conduct extensive prospective multicenter trials that will enable one to obtain adequate data about the diagnostic capabilities of liquid biopsy as well as its use as an instrument for monitoring therapy.

Conclusion

Liquid biopsy shows high diagnostic accuracy through high specificity consistency and superior performance, so we recommend this method as a reliable instrument of diagnosis of non-small cell lung cancer (NSCLC). However, variation in sensitivity and the risk false negatives preclude liquid biopsy as a substitute for tissue biopsy, making it more appropriate for practitioners to use it as a complementary procedure to the tissue biopsy.

References

[1] S. S. Shimamura *et al.*, “Survival past five years with advanced, EGFR-mutated or ALK-rearranged non-small cell lung cancer—is there a ‘tail plateau’ in the survival curve of these patients?,” *BMC Cancer*, vol. 22, no. 1, p. 323, Dec. 2022, doi: 10.1186/s12885-022-09421-7.

[2] C. Chung and G. Umoru, “Prognostic and predictive biomarkers with therapeutic targets in nonsmall-cell lung cancer: A 2023 update on current development, evidence, and recommendation,” *Journal of Oncology Pharmacy Practice*, vol. 31, no. 3, pp. 438–461, Apr. 2025, doi: 10.1177/10781552241242684.

[3] J. A. Nations, D. W. Brown, S. Shao, C. D. Shriver, and K. Zhu, “Comparative Trends in the Distribution of Lung Cancer Stage at Diagnosis in the Department of Defense Cancer Registry and the Surveillance, Epidemiology, and End Results data, 1989–2012,” *Mil. Med.*, vol. 185, no. 11–12, pp. e2044–e2048, Dec. 2020, doi: 10.1093/milmed/usaa218.

[4] T. J. J. de Bitter *et al.*, “Clinical utility of liquid biopsy next-generation sequencing for advanced non-small cell lung cancer in the Netherlands,” *Sci. Rep.*, vol. 15, no. 1, p. 30343, Aug. 2025, doi: 10.1038/s41598-025-13667-z.

[5] B. Da Nam, S. H. Yoon, H. Hong, J. H. Hwang, J. M. Goo, and S. Park, “Tissue Adequacy and Safety of Percutaneous Transthoracic Needle Biopsy for Molecular Analysis in Non-Small Cell Lung Cancer: A Systematic Review and Meta-analysis,” *Korean J. Radiol.*, vol. 22, no. 12, p. 2082, 2021, doi: 10.3348/kjr.2021.0244.

[6] N. Guibert, A. Pradines, G. Favre, and J. Mazieres, “Current and future applications of liquid biopsy in nonsmall cell lung cancer from early to advanced stages,” *European Respiratory Review*, vol. 29, no. 155, p. 190052, Mar. 2020, doi: 10.1183/16000617.0052-2019.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

[7] C. Rolfo *et al.*, "Liquid Biopsy for Advanced NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer," *Journal of Thoracic Oncology*, vol. 16, no. 10, pp. 1647–1662, Oct. 2021, doi: 10.1016/j.jtho.2021.06.017.
[8] P. van der Leest *et al.*, "Detection and Monitoring of Tumor-Derived Mutations in Circulating Tumor DNA Using the UltraSEEK Lung Panel on the MassARRAY System in Metastatic Non-Small Cell Lung Cancer Patients," *Int. J. Mol. Sci.*, vol. 24, no. 17, p. 13390, Aug. 2023, doi: 10.3390/ijms241713390.
[9] I. A. Kim, J. Y. Hur, H. J. Kim, W. S. Kim, and K. Y. Lee, "Extracellular Vesicle-Based Bronchoalveolar Lavage Fluid Liquid Biopsy for EGFR Mutation Testing in Advanced Non-Squamous NSCLC," *Cancers (Basel).*, vol. 14, no. 11, p. 2744, May 2022, doi: 10.3390/cancers14112744.
[10] B. Tomasik, M. Skrzypski, M. Bieńkowski, R. Dziadziuszko, and J. Jassem, "Current and future applications of liquid biopsy in non-small-cell lung cancer—a narrative review," *Transl. Lung Cancer Res.*, vol. 12, no. 3, pp. 594–614, Mar. 2023, doi: 10.21037/tlcr-22-742.
[11] M. J. Page *et al.*, "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews," *International Journal of Surgery*, vol. 88, Apr. 2021, doi: 10.1016/j.ijsu.2021.105906.
[12] E. H. Ragnarsson, G. Reinebo, and S. Alfonsson, "PROSPERO International prospective register of systematic reviews Citation Centrum för psykiatriforskning," 2021. [Online]. Available: https://www.researchgate.net/publication/352889140
[13] P. F. Whiting *et al.*, "QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies," *Ann. Intern. Med.*, vol. 155, no. 8, pp. 529–536, Oct. 2021, doi: 10.7326/0003-4819-155-8-201110180-00009.
[14] B. M. Wiernik and J. A. Dahlke, "Obtaining Unbiased Results in Meta-Analysis: The Importance of Correcting for Statistical Artifacts," *Adv. Methods Pract. Psychol. Sci.*, vol. 3, no. 1, pp. 94–123, Mar. 2020, doi: 10.1177/2515245919885611.
[15] University of Oxford, "OCEBM Levels of Evidence — Centre for Evidence-Based Medicine (CEBM)," University of Oxford.
[16] C. Aggarwal *et al.*, "Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non–Small Cell Lung Cancer," *JAMA Oncol.*, vol. 5, no. 2, p. 173, Feb. 2019, doi: 10.1001/jamaoncol.2018.4305.
[17] B. M. Kim *et al.*, "Role of Circulating Tumor DNA Profiling in Patients with Non-Small Cell Lung Cancer Treated with EGFR Inhibitor," *Oncology*, vol. 100, no. 4, pp. 228–237, 2022, doi: 10.1159/000516813.
[18] S. Kuderer *et al.*, "Lessons learned from routine, targeted assessment of liquid biopsies for EGFR T790M resistance mutation in patients with EGFR mutant lung cancers," *Acta Oncol. (Madr).*, vol. 58, no. 11, pp. 1634–1639, Nov. 2019, doi: 10.1080/0284186X.2019.1645354.
[19] R. B. Lanman *et al.*, "Analytical and Clinical Validation of a Digital Sequencing Panel for Quantitative, Highly Accurate Evaluation of Cell-Free Circulating Tumor DNA," *PLoS One*, vol. 10, no. 10, p. e0140712, Oct. 2015, doi: 10.1371/journal.pone.0140712.
[20] N. B. Leighl *et al.*, "Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non–small Cell Lung Cancer," *Clinical Cancer Research*, vol. 25, no. 15, pp. 4691–4700, Aug. 2019, doi: 10.1158/1078-0432.CCR-19-0624.
[21] P. C. Mack *et al.*, "Spectrum of driver mutations and clinical impact of circulating tumor DNA analysis in non–small cell lung cancer: Analysis of over 8000 cases," *Cancer*, vol. 126, no. 14, pp. 3219–3228, Jul. 2020, doi: 10.1002/cncr.32876.
[22] S. Park *et al.*, "High concordance of actionable genomic alterations identified between circulating tumor DNA–based and tissue-based next-generation sequencing testing in advanced non–small cell lung cancer: The Korean Lung Liquid Versus Invasive Biopsy Program," *Cancer*, vol. 127, no. 16, pp. 3019–3028, Aug. 2021, doi: 10.1002/cncr.33571.
[23] C. P. Paweletz *et al.*, "Bias-Corrected Targeted Next-Generation Sequencing for Rapid, Multiplexed Detection of Actionable Alterations in Cell-Free DNA from Advanced Lung Cancer Patients," *Clinical Cancer Research*, vol. 22, no. 4, pp. 915–922, Feb. 2016, doi: 10.1158/1078-0432.CCR-15-1627-T.
[24] L. E. Raez *et al.*, "Liquid Biopsy Versus Tissue Biopsy to Determine Front Line Therapy in Metastatic Non-Small Cell Lung Cancer (NSCLC)," *Clin. Lung Cancer*, vol. 24, no. 2, pp. 120–129, Mar. 2023, doi: 10.1016/j.cllc.2022.11.007.
[25] A. G. Sacher *et al.*, "Prospective Validation of Rapid Plasma Genotyping for the Detection of EGFR and KRAS Mutations in Advanced Lung Cancer," *JAMA Oncol.*, vol. 2, no. 8, p. 1014, Aug. 2016, doi: 10.1001/jamaoncol.2016.0173.
[26] V. Veldore *et al.*, "Validation of liquid biopsy: plasma cell-free DNA testing in clinical management of advanced non-small cell lung cancer," *Lung Cancer: Targets and Therapy*, vol. Volume 9, pp. 1–11, Jan. 2018, doi: 10.2147/LCTT.S147841.
[27] O. A. Zill *et al.*, "The landscape of actionable genomic alterations in cell-free circulating tumor DNA from 21,807 advanced cancer patients," Dec. 12, 2018. doi: 10.1101/233205.
[28] M. G. O. Fernandes *et al.*, "Clinical Application of Next-Generation Sequencing of Plasma Cell-Free DNA for Genotyping Untreated Advanced Non-Small Cell Lung Cancer," *Cancers (Basel).*, vol. 13, no. 11, p. 2707, May 2021, doi: 10.3390/cancers13112707.
[29] S. Franzi *et al.*, "Liquid biopsy in non-small cell lung cancer: a meta-analysis of state-of-the-art and future perspectives," *Front. Genet.*, vol. 14, Dec. 2023, doi: 10.3389/fgene.2023.1254839.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 11 No. 2 (2026): December
DOI: 10.21070/acopen.11.2026.14501

[30] M. Mlika, C. Dziri, M. M. Zorgati, M. Ben Khelil, and F. Mezni, "Liquid Biopsy as Surrogate to Tissue in Lung Cancer for Molecular Profiling: A Meta-analysis," *Curr. Respir. Med. Rev.*, vol. 14, no. 1, pp. 48–60, Jul. 2018, doi: 10.2174/1573398X14666180430144452.
[31] N. Wang *et al.*, "The Diagnostic Accuracy of Liquid Biopsy in EGFR-Mutated NSCLC: A Systematic Review and Meta-Analysis of 40 Studies," *SLAS Technol.*, vol. 26, no. 1, pp. 42–54, Feb. 2021, doi: 10.1177/2472630320939565.
[32] H. Shen *et al.*, "Potential clinical utility of liquid biopsy in early-stage non-small cell lung cancer," *BMC Med.*, vol. 20, no. 1, p. 480, Dec. 2022, doi: 10.1186/s12916-022-02681-x.
[33] C. Chen, M. P. Douglas, M. V. Ragavan, K. A. Phillips, and J. P. Jansen, "Clinical Validity and Utility of Circulating Tumor DNA (ctDNA) Testing in Advanced Non-small Cell Lung Cancer (aNSCLC): A Systematic Literature Review and Meta-analysis," *Mol. Diagn. Ther.*, vol. 28, no. 5, pp. 525–536, Sep. 2024, doi: 10.1007/s40291-024-00725-x.
[34] W. Li *et al.*, "Liquid biopsy in lung cancer: significance in diagnostics, prediction, and treatment monitoring," *Mol. Cancer*, vol. 21, no. 1, p. 25, Dec. 2022, doi: 10.1186/s12943-022-01505-z.
[35] D. W. Cescon, S. V. Bratman, S. M. Chan, and L. L. Siu, "Circulating tumor DNA and liquid biopsy in oncology," *Nat. Cancer*, vol. 1, no. 3, pp. 276–290, Mar. 2020, doi: 10.1038/s43018-020-0043-5.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo